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EXAMINER	
LAM, ANN Y	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,629	KNOX ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-7, 9-21, 23 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Pines et al., 6,426,058.

Yu discloses performing an assay on a biological species using an assay reagent (col. 40, lines 37-38) containing at least one NMR active nucleus (col. 40, lines 40-45) to perform an assay, said assay reagent being introduced as an initial reagent, formed in situ during the assay or formed as a product of the assay (col. 8, lines 56-59);

and analyzing the assay reagent and/or the assay by NMR for a physical or chemical change in the biological species that is independent of the interaction of the biological species with the NMR active nucleus (i.e., binding between receptor and agent, column 9, lines 8-19; column 40, lines 37-45, and column 41, lines 41-48.)

Examiner notes that the step of "optionally using the NMR data obtained to generate further assay results" in subsection (d) of claim 1 is only an option and thus is not a required limitation in the claims.

As to claims 2 and 3, the NMR active nucleus is ^{13}C or ^{15}N (col. 40, line 45.)

As to claims 4 and 5, the assay reagent is a compound which contains an artificially high concentration of an NMR active nucleus, (i.e., the NMR active nucleus added as a label to a reagent is considered to be artificially high concentration; col. 8, lines 57-58, and col. 40, lines 40-45.) As to claim 5, since the limitation "in 1-10 defined positions" is vague and indefinite (see above), the concentration of the NMR active nucleus in the Yu disclosure is considered to be in the 1-10 defined positions.

As to claim 6, the assay reagent is an organic compound comprising one or more NMR active nuclei associated with a bond which is broken during the course of the assay (i.e., the competitive displacement assay in col. 55, lines 54-56.)

As to claim 7, each NMR active nucleus produces a distinct NMR spectrum as claimed (col. 41, lines 42-44.)

As to claim 9, the assay reagent is a nucleotide, or nucleotide analogue, polynucleotide, amino acid analogue, polypeptide or protein (col. 8 lines 45-59.)

As to claim 10, the assay is a nucleic acid hybridization assay, see column 8, lines 60-67.

As to claim 11, the assay is a binding assay, (column 8, lines 45-59, or column 9, lines 8-19.)

As to claim 12, the assay reagent is a compound labeled with at least one NMR active nucleus (col. 40, lines 37-45.)

As to claim 13, the assay is a binding study using micro-organisms or cultured cells, (column 38, lines 9-12.)

As to claim 28, a kit is disclosed, which comprises an assay reagent containing at least one NMR active nucleus contained in a container (col. 8, line 48.)

Although Yu teaches use of NMR spectroscopy in conjunction with an NMR active nucleus to analyze an assay, Yu does not teach hyperpolarization of the NMR active nucleus.

Pines, like Yu, also teaches use of NMR spectroscopy (col. 1, lines 18-19) and NMR active nucleus such as ^{13}C or ^{15}N (col. 15, lines 39) to analyze a biological sample (col. 12, lines 6-13; and col. 18, lines 61-64.)

Pines teaches further teaches that hyperpolarization of an NMR active nucleus enhances the noble gas magnetic resonance signal (column 1, lines 12-14; col. 18, lines 31-32.)

It would have been obvious to one of ordinary skill in the art to utilize the Pine hyperpolarization analysis technique to analyze the Yu assays, since both Pine and Yu teach that reagents labeled with isotopes such as ^{13}C or ^{15}N can be analyzed by NMR spectroscopy and Pine further teaches that hyperpolarizing the isotopes will enhance the magnetic resonance signal, as would be desirable for obtaining more accurate results.

Moreover, since both Pine and Yu teach use of NMR spectroscopy with the same NMR active nucleus, i.e., ^{13}C or ^{15}N, and Pine specifically discloses that the hyperpolarization technique to enhance NMR analysis can be utilized in a variety of assays, one of ordinary skill in the art would have a reasonable expectation of success

in using the technique of hyperpolarizing the ^{13}C or ^{15}N as the method of analysis as taught by Pine to analyze the Yu screening assays.

As to claim 16, the hyperpolarization is carried out by polarization transfer from a hyperpolarized noble gas (Pines, col. 9, lines 6-10)

As to claim 21, the polarization transfer uses dynamic nuclear polarization (Pines, col. 2, lines 34-37.)

As to claim 23, the hyperpolarization is carried out with the spin refrigeration technique (Pines, col. 8, lines 25-30.)

As to claim 27, the analyzing step is performed in an aerosol or flow-through device applied to aerosol droplets where the well, surface or container is used to contain the assay reagent (Pines, col. 8, lines 21-25.)

As to claims 17 and 18, Yu does not specifically list ^{129}XE or ^{3}He in its exemplary list of isotopes used in conjunction with NMR spectroscopy. Yu does list ^{13}C or ^{15}N in its exemplary list (col. 40, line 45), and Pines also lists ^{13}C or ^{15}N (col. 15, line 39). Pines further discloses that ^{129}XE (col. 9, line 10) or ^{3}He (col. 9, line 7) are also noble gases that can be hyperpolarized for analysis of a sample. It would have been obvious to one of ordinary skill in the art to utilize ^{129}XE or ^{3}He as the hyperpolarized gas in the Yu assay since Pines teaches that ^{129}XE or ^{3}He can also be hyperpolarized and analyzed using NMR spectroscopy.

Also, as to claims 14, 15, 19, 20, 26 and 29, Yu does not disclose the following: the hyperpolarization transfer is repeated to enhance the signal-to-noise ratio (see claim 14); the shortening effect as expressed by the improvement of signal-to-noise per unit

time is a factor of 10 or more compared to known assay techniques without hyperpolarization (see claim 15); the noble gas is in a solution and the viscosity of the solution is at least 1000 mPs (see claim 19); the hyperpolarization transfer is carried out at a temperature of 4.2 K or less in the presence of a magnetic field of at least 1T (see claim 20); the analyzing step is performed by using both NMR spectroscopy and magnetic resonance imaging, and repeating the examination at least once (see claim 26); the NMR analysis step is carried out in the same well or vial or container as the hyperpolarization transfer is carried out (see claim 29.)

Pines does however disclose that the hyperpolarized noble gas may be in liquid, solid or gas phase, see column 8, lines 22, and that the noble gas can be combined with a fluid to form a mixture, see column 8, lines 53-54, and lines 64-67, and that it is desirable to freeze the gas in a magnetic field (see column 8, lines 27-29), and that the result can be analyzed using both NMR spectroscopy and magnetic resonance imaging (see column 8, lines 60-63), that multiple parameters can be detected, and multiple techniques can be employed to collect and manipulate nuclear magnetic resonance data (col. 19, lines 3-5.)

It would have been obvious to provide the noble gas in a solution having the viscosity as claimed, or to hyperpolarize at the temperature and magnetic field as claimed, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233.

Furthermore, it would have been obvious to repeat the analysis steps, and to perform the NMR analysis step in the same well or vial or container as the hyperpolarization transfer is carried out, since it is generally recognized that repeating known steps to obtain further data, or to perform NMR analysis step in the same well as the hyperpolarization transfer is carried out involves only routine skill in the art.

2. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Pines et al., 6,426,058, as applied to claim 1, and further in view of Maupin, 5,834,226.

Yu in view of Pines discloses the invention substantially as claimed, except for analyzing the assay reagent at known time intervals to generate information about a change with time of the assay reagent.

Maupin, like Yu, discloses a biological assay (col. 5, lines 46-52.), and further teaches that analyzing the assay reagent at known time intervals generate information about a change with time of the assay reagent, (i.e., the rate of reaction determined over a time interval, col. 9, lines 57-58), such analysis being useful in determining concentration of a reagent (col. 9, lines 60-64.)

It would have been obvious to one of ordinary skill in the art to analyze an assay reagent at known time intervals as taught by Maupin using the Yu in view of Pines method of analysis of an assay, as would be desirable to determine a concentration of a reagent in an assay as taught by Maupin, as is often desirable by one of ordinary skill in the art in an analysis of assay.

3. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Pines et al., 6,426,058, as applied to claim 1, and further in view of Ardenkjaer-Larson et al., 6,278,893.

Yu in view of Pines discloses the invention substantially as claimed (see above with respect to claim 1), except for the hyperpolarisation of the NMR active nucleus of the assay reagent being carried out by para hydrogen induced polarisation.

Ardenkjaer-Larson, similar to Yu and Pines, discloses an assay using an assay reagent containing an NMR active nucleus such as ^{13}C nucleus (col. 18, line 14), hyperpolarizing the nucleus (col. 18, line 16), and analyzing the assay by NMR, ex vivo (col. 2, lines 10-29.) ("Ex vivo" as disclosed by Ardenkjaer-Larson is considered the same as in vitro, both meaning outside the living body.) Ardenkjaer-Larson further teaches that the hyperpolarisation is carried out by para-hydrogen induced polarization in order to enhance the signal (col. 18, lines 14-20.)

It would have been obvious to one of ordinary skill in the art to utilize para-hydrogen induced polarization as taught by Ardenkjaer-Larson in order to enhance the signal generated by hyperpolarisation of ^{13}C nucleus in the technique taught by Yu in view of Pines, as would be desirable for obtaining more accurate results as taught by Ardenkaer-Larson.

4. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Pines et al., 6,426,058, as applied to claim 1, and further in view of Obremski, 6,110,749.

Yu in view of Pines discloses the invention substantially as claimed (see above with respect to claim 1), except for more than one assay being multiplexed (claim 24), and for the assay being performed in a multispot assay array (claim 25).

Obremski, like Yu, discloses a biological assay, wherein the assay is multiplexed and performed in a multispot assay array (col. 2, lines 66-67; col. 9, lines 19-20, and 32-33.)

It would have been obvious to one of ordinary skill in the art to provide a multiplexed or multispot assay as taught by Obremski using the Yu in view of Pines method of analysis, as would be desirable for simultaneous assays as taught by Obremski, such simultaneous assays providing the advantage of allowing more assays to be performed quickly.

Response to Arguments

Applicant's arguments filed February 17, 2005 have been fully considered but they are not persuasive.

Applicant argues on page 9 and bottom of page 10 that although Yu mentions the use of isotopically labeled reagents, it is not clear how Yu intends that these should be used. Examiner points to column 40, lines 36-45, which discloses that the detection of an interaction between an agent and a receptor can be accomplished through

techniques well known in the art, and that use of radioactive isotopes as labels in conjunction with techniques well known in the art such as centrifugation, chromatography, electrophoresis and spectroscopy is contemplated. Yu then further discloses in column 40, lines 46-51, that for example if an agent can bind to the receptor of the present invention, the binding can be detected by using radiolabeled agent or radiolabeled receptor. Thus, it is clear that the radioactive isotopes are used as labels to detect binding.

Applicant also argues on page 9 that the cited passage on page 8 relates to an immunoassay and is a completely different assay from that described at column 40 as a different interaction is detected. Thus, Applicant asserts that it is improper to combine these two passages. In response, Examiner points out that column 40 describes a binding assay, which encompasses immunoassays.

Applicant also argues on page 10 that Pines does not disclose a method which includes the step of analyzing the assay reagent and/or the assay by NMR for a physical or chemical change in a biological species that is independent of the interaction of the biological species with the NMR active nucleus. In response, Examiner notes that Examiner describes in the rejection above that Yu discloses these limitations.

Applicant also argues on page 11 that Maupin does not relate to an assay in which a physical or chemical change in a biological species is monitored by NMR and thus is not relevant. Examiner asserts that Maupin is relevant in teaching the analysis of biological assays.

Applicant also argues on page 12 that Ardenkjaer-Larson et al. does not supply the missing features since it fails to disclose an analysis of a physical or chemical change in a biological species that is independent of the interaction of the biological species with the NMR active nucleus. Examiner notes that Examiner describes in the rejection above that Yu discloses these limitations.

Applicant also argues on page 12 that Obremski does not include detection of NMR and thus is not relevant to the method of the present invention, which detection is NMR. Examiner asserts that Obremski is relevant in teaching the analysis of biological assays.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on M-Sat 11-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A.L.

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